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Extrapulmonary Pneumocystosis

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INTRODUCTION

Prior to the epidemic of infection with the human immunodeficiency virus type 1 (HIV-1), *Pneumocystis carinii* infections in humans were infrequently observed and extrapulmonary infection was rare. The HIV-1 epidemic was accompanied by a dramatic increase in the most common opportunistic infection and disease in this patient population, *P. carinii* pneumonia (PCP), and case reports of extrapulmonary *P. carinii* infection, although still rare, began to appear with increasing frequency. Placed in perspective, 16 cases of extrapulmonary *P. carinii* infection in non–HIV-1–infected individuals were reported from 1954 until 1996, whereas at least 90 cases of extrapulmonary *P. carinii* infection in HIV-1-infected individuals have been published since 1982 (Fig. 1); in contrast, PCP was the indicator infection for 20,235 newly diagnosed cases of AIDS in the United States as reported to the Centers for Disease Control and Prevention from the beginning of the HIV-1 epidemic until 1993 (62).

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The total number of cases of HIV-associated extrapulmonary pneumocystosis tabulated in reviews and published between 1990 and 1992 (85, 104, 116, 127, 137) was insufficient to answer a number of relevant questions, the most important of which was whether primary or secondary aerosolized pentamidine for PCP prophylaxis predisposed to extrapulmonary disease. Subsequent case reports not only have provided us with an expanded total number of cases of HIV-associated extrapulmonary pneumocystosis but also have included sufficient clinical information to address some of the unanswered questions posed in the previously published reviews.

HISTORICAL BACKGROUND

Although microscopically observed and described as early as 1909, *P. carinii* was not recognized as a human pathogen until the 1950s. Chagas first observed pneumocystis organisms in the lungs of guinea pigs coinfected with *Trypanosoma cruzi* in 1909; observation of pneumocystis organisms in the lungs of a patient who had died of Chagas' disease led to his erroneous conclusion that these organisms represented a stage in the trypanosome life cycle (14). Shortly thereafter, Carini published his observations of pneumocystis-like organisms in

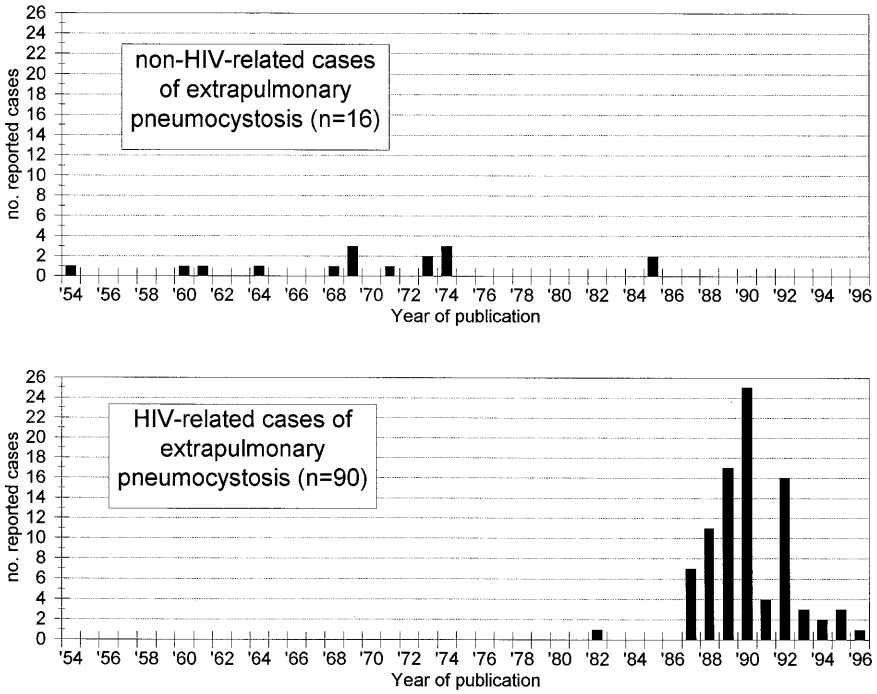

FIG. 1. Number of reported cases of extrapulmonary pneumocystosis relative to the year of publication.

Trypanosoma lewisi-infected rat lung tissue (10). Subsequently, Delanoe and Delanoe (24) made the critical observation that organisms present in the lungs of rats with PCP were morphologically similar to those present in the *T. lewisi*-infected rat lung tissue and previously described by Carini. They concluded that pneumocystis was a unique organism and assigned it a genus name of *Pneumocystis* (*pneumo* = lung, *cyst* = cyst-like structures) and a species name of *carinii*, in honor of A. Carini (24, 54).

In the 1950s, sporadic outbreaks of interstitial plasma cell pneumonia were occurring among premature and malnourished (i.e., marasmic) children housed in nursing homes in Central and Eastern Europe after World War II. In 1952, Vanek and Jirovec reported that the lungs of marasmic infants with interstitial plasma cell pneumonia contained *P. carinii*, and thereby linked the organism with human disease (130). In 1955, Weller observed that corticosteroid treatment of susceptible rats resulted in PCP (139), and in 1966, Frenkel et al., recognizing that latent pulmonary infection was widespread in rodents, defined the laboratory parameters for establishing experimental infection (37). Shortly thereafter, PCP was recognized as an opportunistic pathogen for humans who were immunosuppressed by a variety of iatrogenic or naturally occurring diseases. Conditions predisposing to PCP included cytotoxic and corticosteroid therapy of malignancies (e.g., lymphoma, chronic myelogenous or lymphocytic leukemia, Hodgkin's disease, solid tumors), corticosteroid therapy of rheumatological disorders, iatrogenically induced immunosuppression prior to solid organ or bone marrow transplantation, congenital immunodeficiency (e.g., hypogammaglobulinemia), Cushing's syndrome (hypercorticosteroidism), protein calorie malnutrition (marasmus), and old age.

TAXONOMY

P. carinii is a unicellular eukaryotic organism whose phylogeny has not been determined with certainty. *P. carinii* was originally grouped with the protozoa, but it has a number of features in common with fungi (32, 126, 134). *P. carinii* and fungi have similar cyst wall ultrastructures, have mitochondria with lamellar cristae (protozoan mitochondria have tubular cristae), and have cyst forms containing intracystic bodies resembling those of ascospores formed by the ascomycetes (112, 113, 128). The 16S rRNA subunit of *P. carinii* is most homologous to that of ascomycetes (31, 124, 125), while the 5S rRNA is most homologous to that of primitive zygomycetes (138). The β-tubulin gene is 89 to 91% homologous to that of the filamentous fungi (27, 29). The protein synthesis elongation factor, EF-3, and thymidylate synthase of *P. carinii* are most homologous to those of the ascomycetes, and thymidylate synthase and dihydrofolate reductase activities are contained on two separate proteins (in contrast, protozoa produce a single bifunctional protein) (30, 33). A 6.8-kb fragment of mitochondrial DNA that encodes apocytochrome B, NADH dehydrogenase subunits 1, 2, 3, and 6, cytochrome oxidase subunit II, and a small subunit of rRNA had an average similarity of 60% to that of fungi (but an average similarity of only 20% to that of protozoa) (95, 125).

In contrast, ergosterol, the sterol found in the membranes of most fungi, has not been detected in *P. carinii*. Perhaps the lack of ergosterol may account for the clinical inefficacy of commonly used antifungal agents that depend on binding to ergosterol (e.g., amphotericin B) or inhibiting the synthesis of ergosterol (e.g., imidazole and triazole antifungal agents) (32, 101).

EPIDEMIOLOGY

Natural Reservoir

The natural reservoir of *P. carinii* remains unknown. It is thought to be widespread in the environment, and a recent study demonstrated *P. carinii* DNA sequences in spores found in air samples (133). Detection of *P. carinii* in the lungs of a variety of immunodeficient mammals (e.g., humans, primates, rodents, hares, ferrets, cats, dogs, and horses) demonstrated its pathogenicity for multiple species and provided further evidence that it is pervasive in the environment (55, 56).

Serologic studies also suggest that *P. carinii* is ubiquitous in the environment. Human contact with *P. carinii* and development of anti-pneumocystis immunity is thought to occur at an early age in most humans. Pifer et al., using an indirect fluorescent-antibody test, observed that 83% of 4-year-old children had antibody to *P. carinii* (91). Peglow et al., using immunoblotting techniques, observed antibody directed against the 40-kDa major antigen of human-derived *P. carinii* in 94% of children aged 2.5 years or older (89). There was no difference by geographical area in the prevalence of antibodies detected by this immunoblot method (89).

Strain Differences

Different varieties, perhaps even different species, of *Pneumocystis* exist. Although *Pneumocystis* spp. recovered from mammalian sources (e.g., rats and humans) are morphologically indistinguishable, there are significant differences between rat- and human-derived *Pneumocystis* spp. in surface antigens, karyotypes, and the nucleic acid sequences of a variety of cloned genes (52, 68, 73, 117, 123). DNA sequences obtained to date from different animal sources have permitted subgrouping of *P. carinii* strains into *P. carinii* f. sp. *carinii* (rat derived), *P. carinii* f. sp. *hominis* (human derived), and *P. carinii* f. sp. *rattus* (a second strain of rat-derived *P. carinii* originally detected in immunosuppressed rats housed in animal care facilities in the United States) (22).

Transmission

Although transmission of *P. carinii* among rodents occurs through the air, it is unlikely that infected rodents serve as a zoonotic reservoir for human infection, since rat-derived *P. carinii* strains are distinct from human-derived strains (117, 123). Although the infectious form of *P. carinii* is not known, the freshly released intracystic body (or the small trophic form) is 1 to 3 μm, the same size as other pulmonary pathogens (e.g., tubercle bacilli) that are successfully spread deep into the lung via aerosolization.

The high seroprevalence of antipneumocystis antibodies present in young children has led to the assumption that *P. carinii* infection in immunosuppressed adults and older children is caused by reactivation of presumably latent disease. The following evidence, however, suggests that newly acquired infection can occur and that reactivation of latent infection may not necessarily account for all cases of PCP. First, numerous epidemic-like clusters of PCP have occurred in either immunodeficient or immunocompetent adults in different geographical regions (17, 35, 58, 118). Second, studies by highly sensitive detection methods (e.g., monoclonal antibody or PCR techniques) have failed to detect latent infection in immunocompetent humans (77, 80, 90, 135). Third, not only did immune system reconstitution of immunodeficient mice with naturally acquired *P. carinii* rid them of infection, but also histologic methods and PCR failed to detect residual *P. carinii* in their lungs (16). Furthermore, their disease did not recur following $CD4^+$ lymphocyte depletion and corticosteroid treatment (16). These findings were supported by similar observations of spontaneous *P. carinii* clearance within 1 year in the lungs of 75% of rats (i.e., no "residual" organisms detectable by histologic testing or PCR) with corticosteroid-induced PCP (131). Fourth, both fluorescent monoclonal antipneumocystis antibody techniques and PCR detection methods have failed to detect *P. carinii* in the lungs of AIDS patients without PCP (80).

Despite this evidence suggesting that new acquisition of *P. carinii* might occur later in life, the route of transmission remains unknown. Although rat studies have convincingly demonstrated airborne transmission of *P. carinii* (53, 57), there is insufficient evidence to demonstrate that person-to-person transmission occurs. Thus, routine isolation of patients with PCP is not currently recommended.

Vertical transmission of *P. carinii* occurs in animals and was recently documented to occur in humans also. Vertical transmission in rats was demonstrated by *P. carinii* infection in the offspring of cesarean-delivered germfree rats (92). Vertical transmission in humans was concluded for a single case of a stillborn infant born to an HIV-infected mother where *P. carinii* was detected in the infant's lungs and in the placental villi (81).

Host Immunity

The host immune system plays a critical role in suppressing *P. carinii* and maintaining a presumably "latent" state of infection in the immunocompetent host. T cells are highly implicated in the immune system processes that govern the suppression of latent *P. carinii* infection. Adoptive T-cell transfer in animals confers a protective immune response to *P. carinii* infection in animals (39). Cyclosporine, an inhibitor of T-cell-mediated immunity, induces PCP in animals and human transplant recipients. The high frequency of PCP in HIV-infected individuals, typically those with a profound defect in their T-cell-mediated immunity (i.e., peripheral $CD4^+$ lymphocyte count of $<200/\mu l$), highlights the critical protective role of the T-cell arm of the host immune system.

Of note, if new acquisition of *P. carinii* later in life can cause disease, it implies that exposure early in life may not provide protective immunity against subsequent infection (with presumably different strains?). Alternatively, exposure to a different strain of pneumocystis or lack of exposure during childhood could result in disease in adulthood.

Events in Infection

The physiologic events occurring immediately after infection with *P. carinii* have been defined in rat model systems. The trophic form of *P. carinii* uses the host proteins to adhere to the alveolar type 1 pneumocyte as follows: fibronectin serves as a bridge between the principal surface antigen of *P. carinii* and host cells, and the alveolar macrophage mannose receptor binds to mannose residues on the *P. carinii* surface glycoprotein (34, 99, 142).

EXTRAPULMONARY PNEUMOCYSTOSIS

Incidence

Overall incidence. While *P. carinii* pneumonia accounted for 20,519 (33%) of the 61,375 cases for which an AIDS-defining opportunistic infection was definitively demonstrated from the beginning of the HIV-1 epidemic until 1993 (62), it has been estimated that 66 to 85% of all HIV-1-infected individuals will have at least one episode of PCP during their lifetime (13, 64).

Although the incidence of extrapulmonary pneumocystosis has been difficult to determine and estimates vary, it is agreed that the incidence is low, regardless of whether HIV-1 infection is present. Prior to the HIV-1 epidemic, a review of more than 200 autopsies of patients with PCP failed to reveal any with extrapulmonary *P. carinii* (4), and another autopsy review revealed that only 1 (2%) of 46 immunodeficient children with PCP had extrapulmonary pneumocystosis (in the lymph nodes and thymus) (9).

A number of studies have attempted to define the incidence of extrapulmonary pneumocystosis in HIV-infected individuals. In their 1991 review, Cohen and Stoeckle calculated an incidence of 0.06% based on the fact that fewer than 50 cases of extrapulmonary *P. carinii* infections had been reported during a period when more than 80,000 cases of PCP in HIV-infected individuals had occurred (18). In his 1990 review of extrapulmonary pneumocystosis, Raviglione calculated an incidence of 0.53% for Cabrini Hospital in Manhattan based on his knowledge of 5 cases of extrapulmonary pneumocystosis that had occurred during the same period in which 940 episodes of PCP had been diagnosed (104). A much higher incidence was reported by Cote et al., who detected extrapulmonary pneumocystosis in 4 (2.5%) of 161 AIDS patients who died and were examined at autopsy at New York's Memorial Hospital between 1980 and 1988 (19).

Incidence in HIV-infected patients receiving prophylactic aerosolized pentamidine. Aerosolized pentamidine prophylaxis for primary or secondary PCP in HIV-1-infected individuals was demonstrated to be highly effective and was widely used in the late 1980s and early 1990s. It was at approximately the same time that case reports of extrapulmonary pneumocystosis were being published. Concern was raised that the incidence of extrapulmonary pneumocystosis might increase with continued use of aerosolized pentamidine, since this route of delivery did not protect against systemic disease; furthermore, despite its relative clinical inefficacy, aerosolized pentamidine remains in widespread use because of the high frequency of toxic side effects associated with the more effective trimethoprim-sulfamethoxazole (TMP-SMX) or dapsone systemic prophylaxis for PCP.

The overall incidence or prevalence of HIV-associated extapulmonary pneumocystosis cannot be accurately estimated. The use of only published reports to establish its incidence most probably underestimates its true incidence. Northfelt et al., in fact, reported that an informal survey of physicians who cared for large numbers of AIDS patients revealed "numerous cases" that had not been published (85). Similarly, publication bias negatively influences the total number of cases published, since increased awareness of this unusual clinical entity over recent years has most probably restricted the publication of additional cases unless novel clinical features were present. Autopsy studies, on the other hand, might tend to overestimate the incidence of extrapulmonary pneumocystosis due to the thorough examination of organs harboring infections that are clinically inapparent. Lastly, since the total number of PCP cases reported is an underestimate, the prevalence of extrapulmonary pneumocystosis based on the number of published cases relative to the total number of PCP cases reported would be an overestimate.

Despite the wide variability in the calculated or observed incidence of extrapulmonary pneumocystosis, there is consensus that the disease is relatively rare. Six studies assessing the efficacy of various prophylactic regimens for PCP reported their accrued incidence of extrapulmonary pneumocystosis. One of the original studies demonstrating the efficacy of aerosolized pentamidine for either primary or secondary PCP prophylaxis reported a single case of extrapulmonary pneumocystosis in 408 enrolled participants (0.2% incidence) (70). The extrapulmonary pneumocystosis was discovered as calcified splenic and hepatic granulomas at the time of autopsy, 11 months after the study had stopped and 7 months after the patient had received his last dose of aerosolized pentamidine off study. Wasting syndrome was the cause of this patient's death, and the contribution of his extrapulmonary pneumocystosis to his death was unclear. Hirschel et al. (51), in their case-controlled 18-month study of aerosolized pentamidine for primary PCP prophylaxis, failed to identify a single case of extrapulmonary pneumocystosis in 114 patients who had received aerosolized pentamidine; autopsy examination of 12 patients who died during this study failed to demonstrate asymptomatic extrapulmonary pneumocystosis. Girard et al. did not report any cases of extrapulmonary pneumocystosis in 176 patients who had received aerosolized pentamidine as part of a study to evaluate its efficacy for primary PCP prophylaxis (44). Bozzette et al. did not report any cases of extrapulmonary pneumocystosis in 278 patients who had received aerosolized pentamidine as part of a 48-month study to compare its efficacy with that of systemic therapy with TMP-SMX or dapsone (7). Noskin and Murphy (86) reported extrapulmonary pneumocystosis in 3 (6.7%) of 45 patients in their cohort who had received prophylactic aerosolized pentamidine for >18 months, compared with none of 82 patients who had received the same therapy for <18 months (all 3 patients with extrapulmonary pneumocystosis had advanced HIV-1-related disease, as indicated by profound immunosuppression and hypoalbuminemia [mean peripheral $CD4^+$ lymphocyte count of 6.3/μl, mean albumin level in serum of 2.5 g/dl]). Witt et al. reported 1 (1.8%) case of extrapulmonary pneumocystosis in 55 patients who were receiving primary prophylaxis with aerosolized pentamidine and 1 (1.6%) case in 68 patients who were receiving aerosolized pentamidine for secondary PCP prophylaxis; in contrast, they observed no cases in 116 patients receiving TMP-SMX for PCP prophylaxis (141).

In summary, although patient follow-up in these studies may have been too short to adequately enumerate cases of extrapulmonary pneumocystosis, the cumulative reported incidence of extrapulmonary disease in patients receiving prophylactic aerosolized pentamidine was nonetheless low (i.e., 6 reported cases in a total of 1,099 patients, for an overall incidence of 0.5%).

Incidence in HIV-infected patients receiving systemic antipneumocystis therapy. Although aerosolized pentamidine is effective for either primary or secondary PCP prophylaxis, its high cost (~$1,185/year; dosed at 300 mg monthly) relative to either TMP-SMX ($60/year; dosed at 160/800 mg daily) or dapsone ($60/year; dosed at 100 mg daily) has rendered it a second-line therapy for use only in patients who cannot toler-

ate TMP-SMX or dapsone (63). Although it was believed that disseminated disease should not occur in patients receiving systemic prophylaxis, at least two cases of extrapulmonary pneumocystosis have been reported in this group of patients (11, 97). Both patients had received dapsone-pyrimethamine prophylaxis—one with 100/25 mg twice weekly for 7 months, and the other with dapsone (100 mg weekly) and pyrimethamine (25 mg twice weekly) for 9 months. Peripheral $CD4^+$ lymphocyte counts were not reported for either patient. Both patients presented with concurrent PCP, both died within 1 week of presentation, and postmortem examination revealed *P. carinii* in either lymph nodes (tracheobronchial, celiac, and para-aortic) or liver.

Sites of Extrapulmonary Pneumocystosis

Extrapulmonary pneumocystosis has occurred in a variety of organs and tissues. All cases of extrapulmonary pneumocystosis discussed in this review were included based on diagnoses made by the authors of the original reports. Many of the published cases lacked significant clinical information at the time of or subsequent to presentation, as reflected in the following summaries.

Non-HIV-associated extrapulmonary pneumocystosis. (i) Clinical presentation. Of 16 patients previously reported to have extrapulmonary pneumocystosis, 13 had underlying diseases; 6 of these patients were children (4 with congenital hypogammaglobulinemia [4, 9, 69, 72], 1 with thymic alymphoplasia [102], 1 with cachexia [143]), and 7 were adults (2 with hypogammaglobulinemia [48, 59], 1 with chronic myeloid leukemia [4], 1 with Hodgkin's disease [110, 111], 1 with non-Hodgkin's lymphoma [110, 111], 1 with malignancy [100], and 1 with a renal transplant [3]). No underlying diseases predisposing to the development of extrapulmonary pneumocystosis were present in the remaining three patients (2, 4, 49).

Of the 16 patients, 13 presented with or had a recent episode of PCP; of the remaining 3 patients, 1 presented with fatigue, 1 presented with pancytopenia, and the presenting condition for the last was not stated. For the 13 patients with concurrent PCP, extrapulmonary infection was limited to the hilar or tracheal lymph nodes in 5 but was widespread in various combinations of two or more noncontiguous organs or sites (i.e., spleen, thymus, lumens of blood vessels, liver, bone marrow, adrenals, brain, kidneys, gastrointestinal tract, heart, liver, thyroid, pericardium, and hard palate) in the other 8. The patient who presented with fatigue had widespread extrapulmonary disease (i.e., in the liver, spleen, bone marrow, and lymph nodes), whereas the patient who presented with pancytopenia had extrapulmonary disease limited to the bone marrow.

(ii) Clinical significance and outcome. Of the 16 patients with extrapulmonary pneumocystosis, 10 died within 2 months of their presentation with PCP (mean, 22.3 days; range, 2 to 56 days). (The remaining 6 patients also died, but their time of death relative to their diagnosis was not reported.)

Extrapulmonary pneumocystosis was not clinically evident or recognized before death in at least 9 of the 16 patients. Of the four patients in whom disseminated disease was clinically significant prior to death, extrapulmonary *P. carinii* infection was diagnosed prior to death in only two (both had extrapulmonary disease limited to the bone marrow; one patient presented with PCP, and the other presented with pancytopenia).

HIV-associated extrapulmonary pneumocystosis. Extrapulmonary pneumocystosis in HIV-infected patients (Table 1) is clinically distinct from that in non-HIV-infected individuals in the following ways. First, disease in HIV-1-infected individuals that was apparently restricted to the ear or eye had a better prognosis; disease limited to the eye or ear was not observed in any non-HIV-infected individuals. Second, all reported HIV-infected individuals with extrapulmonary pneumocystosis had clinically evident disease with symptoms referable to the affected organ or tissue, whereas extrapulmonary pneumocystosis in non-HIV infected individuals was often clinically inapparent.

A few other generalizations can be made about extrapulmonary pneumocystosis in HIV-infected individuals. First, for those few patients for whom both survival and the peripheral $CD4^+$ lymphocyte count were reported, survival was not directly correlated with the $CD4^+$ count (Fig. 2). Second, despite increasing awareness of the possibility of disseminated disease over the past decade, there has not been an appreciable increase in survival (Fig. 3). Third, disseminated disease is not restricted to patients who receive aerosolized pentamidine for primary or secondary PCP prophylaxis (see above). Fourth, concurrent or prior PCP is often not present at the time of presentation. Fifth, there is no correlation between extrapulmonary pneumocystosis and specific risk categories for HIV acquisition.

The following discussion of HIV-associated extrapulmonary pneumocystosis is grouped into cases apparently restricted to a single site or organ and those involving widespread disease (i.e., disease occurring in two or more noncontiguous sites). This grouping is somewhat flawed, since patients with disease seemingly limited to a single symptomatic site often did not undergo additional studies to investigate whether other organs might also harbor silent infection. Similarly, patients examined at autopsy because of a rapid clinical deterioration often had pneumocystis detected at sites where infection was not suspected clinically.

(i) Restricted to a single site. *(a) Ear.* Nine cases of extrapulmonary pneumocystosis limited to the ear have been reported (Table 1, cases 1 to 9). At least two patients had prior bouts of PCP, and at least one received secondary PCP prophylaxis with aerosolized pentamidine for 5 months. At least four patients had never had a prior episode of PCP or had received any prior aerosolized pentamidine prophylactic therapy. Peripheral $CD4^+$ lymphocyte counts were not reported, but three patients had been previously diagnosed with AIDS and another three were described as HIV seropositive without mention of symptoms suggestive of AIDS-related complex (ARC).

Two cases were limited to the external auditory canal, and seven were limited to the middle ear. Symptoms reported for eight of the nine patients at the time of presentation included hearing loss, with a mass lesion (often a polyp), otorrhea, or pain. The masses or polyps were attached at multiple sites in the auditory canal or were found protruding through the tympanic membrane; extension to the mastoid and destruction of the ossicles was reported for one patient (137). Histologic examination of biopsy specimens of the masses or polyps revealed numerous pneumocystis cysts and trophozoites embedded in an eosinophilic matrix.

All the patients were successfully treated with TMP-SMX (two patients were also concurrently treated with norfloxacin or trimetrexate), with virtually complete resolution of symptoms and mass lesions. Two patients subsequently developed PCP within 6 weeks and 14 months, respectively, of their initial otic pneumocystosis.

TABLE 1. Clinical features of previously published cases of extrapulmonary pneumocystosis[a]

Case no.[b]	HIV diagnosis	Risk factor	Peripheral CD4 count (no/μl)	Previous PCP	Previous AP (duration [mo])	Concurrent PCP	Symptom(s)	Site	Drug therapy	Survival (days)	Other opportunistic infections or cancers	Reference
1		IVDU		No	No	No	Hearing loss, otorrhea	Ear (external auditory canal)	TMP-SMX	Survived	MTb	8
2	HIV^+			No	No	No	Hearing loss	Ear (middle; aural polyp, protruding through tympanic membrane)	TMP-SMX	Survived		65
3	HIV^+			No	No	No	Hearing loss	Ear (middle; aural polyp, protruding through tympanic membrane)	TMP-SMX	Survived		65
4*	AIDS	Homo		No	No	No	Hearing loss, pain, discharge	Ear (middle; mass perforating tympanic membrane)		548	CMV, HSV, PML	137
5	AIDS	Bisex		Yes (×4)	Yes (5)	No	Hearing loss, pain	Ear (middle)	TMP-D + norfloxacin			119
6	AIDS	Bisex		Yes (mult)				Ear (middle), mastoid				42
7					No	No	Hearing loss	Ear (external auditory canal)	TMP-SMX	Survived		115
8	HIV^+	Homo			No	No	Hearing loss	Ear (middle), mastoid	TMP-SMX + trimetrexate	Survived	PCP 14 mo later	42
9			187			No	Hearing loss, pain, drainage	Ear (middle; polyp in canal perforating tympanic membrane)	TMP-SMX	Survived	PCP 6 wk later	114
10			12	No	No	No		Eye (choroid)	AP	Alive at 21 mo		116
11			36	Yes	Yes (26)	No		Eye (choroid)	None	14		116
12				Yes	Yes (9)	No	Blurred vision (both eyes)	Eye (choroid)	i.v. P	Survived		26
13				Yes	Yes (5)	No	Intermittent blurred vision for 3 wk	Eye (choroid)	TMP-SMX	Survived		26
14	AIDS	IVDU		Yes (×1)	Yes (8)	No	Visual loss (right eye)	Eye (choroid)	TMP-SMX	Survived	CMV	36
15			10	Yes	Yes (10)	No		Eye (choroid)	i.v. P, D-TMP	548		116
16	AIDS			Yes	Yes (10)	No		Eye (choroid)	D-TMP	334		116
17	AIDS		38	Yes	Yes (1)	No		Eye (choroid)	D-TMP	Alive at 10 mo		116
18	AIDS	IVDU		Yes	Yes (8)	No	Conjunctival and oral KS	Eye (choroid)	i.v. P	10	CMV, KS	103
19	AIDS				Yes (8)	No	Bilateral pleural effusions	Eye (choroid)	i.v. P → D	Alive at 4 mo	MAC	109
20	AIDS	Homo		Yes (mult)	Yes	No	Retinal detachment secondary to CMV retinitis	Eye (choroid)	i.v. P → D	Alive at 1 mo	CMV	109
21	AIDS			Yes (×3)	Yes			Eye (choroid)			CMV	109
22	AIDS			Yes (×3)			No ocular symptoms	Eye (choroid)		Alive at 6 mo		109
23	AIDS	Homo		Yes (×1)	Yes (24)	No	Thyromegaly	Thyroid	TMP-SMX	Survived		104
24	AIDS	IVDU			No	No	Thyromegaly	Thyroid	TMP-SMX	Survived	*C. neoformans*	4

25*	AIDS	Homo					Hypothyroidism	Thyroid	None	42	PCP 6 weeks later→death; widespread *P. carinii* noted at autopsy	78
26	AIDS			No	No	No	Thrombocytopenia	Spleen	i.v. P	Survived		93
27	AIDS	Homo			Yes (12)	No	Splenomegaly	Spleen	i.v. P	Survived	MAC, *C. neoformans*, candidiasis	94
28				Yes (×1)	Yes (20)	No	Chest wall discomfort	Pleural effusion	TMP-D → i.v. P	365	*C. neoformans*	60
29	AIDS	Homo		Yes (×2)	No	No	Extreme weakness	Bone marrow	i.v. P	30	CMV	105
30	AIDS	Homo	49	No	Yes (30)	No	Muscle tenderness	Right thigh muscle	TMP-SMX	150	CMV, MAC	88
31*	AIDS				Yes (6)	No		Meninges, cerebral cortex		1	*C. neoformans*	85
32	AIDS	Homo					Diarrhea, fever, chills	Cecum, descending and sigmoid colon	i.v. TMP-SMX → i.v. P		MAC, KS; ocular pneumocystosis hospital day 16	5
33	ARC				No	No	Acute abdominal pain	LN, GI tract, vessels	i.v. TMP-SMX	Survived		12
34	AIDS	Homo		Yes	Yes	No	Dysphagia, diarrhea, anasarca	Bone marrow, GI tract	i.v. P	7		106
35	AIDS		56	Yes	Yes (12)	No	Fever, increasing abdominal girth	Bone marrow, ascites, urine	TMP-SMX	18		75
36	AIDS		10	Yes (×2)	Yes (8)	No	Pancytopenia	Bone marrow, eye (choroid)	TMP-D	183	MAC, HSV, KS	85
37	AIDS	Homo	17		Yes (9)	No	Fever, weight loss, enlarging liver	Liver, LN	i.v. P, TMP-D	Survived		121
38	AIDS	IVDU		Yes (×1)	Yes (15)	No	Abdominal distension, fevers, lower-extremity edema	Liver, eye (choroid)	i.v. P, TMP-SMX	Alive at 8 mo		107
39				Yes	Yes (15)	No		Liver, bone marrow, eye (choroid)	i.v. P	30		116
40	AIDS		9	Yes (×2)	Yes (25)	No	Ascites, fever, decreased visual acuity	Liver, eye (choroid)	i.v. P	18		46
41	AIDS	Homo	7	No	Yes (25)	No	Fever, fatigue, weight loss, cough	Liver, spleen	i.v. TMP-SMX → i.v. P	Alive at 17 mo	KS	67
42	AIDS	Homo		Yes (×2)	Yes (11)	No	Abdominal pain, fever, night sweats	Liver, spleen, LN	Trimetrexate	90	CMV	98
43*	AIDS			Yes (×2)	Yes (10)	No	Fever, chills, night sweats	Liver, spleen, LN, kidneys	None	7		47
44*	AIDS		9	Yes (×2)	Yes (17)	No	Increasing abdominal girth	Lungs, liver, spleen, thyroid, kidneys, small bowel, ascites	i.v. P → primaquine + clindamycin	14		75
45*			3	Yes	Yes (17)	Yes (prob)		All organs at autopsy	None	14		116
46*	AIDS		3		No (stopped 12 mo PTA)	Yes (in mother)	Cough, dyspnea, fever	Lungs (maternal and fetal), placental villi	TMP-SMX + prednisolone	21		81
47	HIV^+	Homo		Yes (×1)	Yes (2)	Yes (probably)	Fever, cough, dyspnea	Lungs, LN	i.v. P	Survived	MAC	18

TABLE 1—*Continued*

Case no.[b]	HIV diagnosis	Risk factor	Peripheral CD4 count (no/μl)	Previous PCP	Previous AP (duration [mo])	Concurrent PCP	Symptom(s)	Site	Drug therapy	Survival (days)	Other opportunistic infections or cancers	Reference
48*	ARC	Tx			No	Yes		Lungs, LN, GI tract, thyroid, diaphragm	TMP-SMX	70		76
49	AIDS		8	Yes	Yes (9)	Yes		Lungs, LN, eye (choroid)	i.v. T → D-TMP	548		116
50*	ARC				No	Yes	Weight loss, dyspnea, arthralgias, malaise, anorexia	Lungs, bone marrow	TMP-SMX	60	CMV, candidiasis	50
51	HIV$^+$			No	No	Yes	Respiratory failure	Lungs, bone marrow		20		111
52	AIDS		74	No	Yes (10)	Yes	Increasing abdominal girth	Lungs, bone marrow, ascites	TMP-SMX + prednisolone	14		75
53	AIDS	Homo		Yes (×4)	Yes	Yes	Recurrent PCP	Lungs, eye (choroid)	i.v. P	334	CMV, MAC	109
54	AIDS			Yes	Yes	Yes	Polyarthralgia, massive lower-extremity edema, dyspnea	Lungs, eye (choroid)	None	7	CMV, KS, candidiasis	103
55		Homo			Yes	Yes		Lungs, eye (choroid)	i.v. P	152	CMV, KS	38
56	HIV$^+$				Yes (10)	Yes		Lungs, eye (choroid)	i.v. P	Alive at 4 mo	KS	38
57	AIDS	IVDU		Yes (×5)	Yes	Yes	PCP related	Lungs, eye (choroid)	i.v. T → D	Alive at 1 yr		109
58	AIDS			Yes	No	Yes	Hearing loss, dyspnea	Lungs, ear (external auditory canal, bilateral; left middle ear)	TMP-SMX	Survived	*C. neoformans*, KS	20
59	ARC	Homo	10	No	No	Yes	Fever, cough, otalgia, otorrhea	Lungs, ear (external), paraspinous masses (×3, thorax)	TMP-D, AP	Survived	Candidiasis	85
60*		IVDU		No	No (D/pyri, 100/25 qw × 9 mo)	Yes	Pneumonia	Lungs, liver	i.v. cotrimoxazole, steroids, imipenem	4	*M. kansasii*	97
61	AIDS	Homo		Yes (×1)	Yes (9)	Yes	Cough, right-sided pleuritic chest pain, fever, shortness of breath	Lungs, liver	i.v. P	Survived		96
62*	AIDS	Homo		Yes (×3)	Yes (3)	Yes	Fever, chest pain, lethargy	Lungs, liver, spleen, LN, bone marrow, kidney, adrenals, heart, skin, trachea, pituitary	P	8	CMV, MAC, KS	127
63*	AIDS	IVDU		Yes (×2)	No	Yes	Dysphagia	Lungs, liver, spleen, LN, bone marrow, kidneys, adrenals, heart, pancreas, GI tract	i.v. P	24		45
64*	AIDS	Homo		Yes (mult)	Yes	Yes	Fever, chest pain, edema	Lungs, liver, spleen, LN, bone marrow, kidneys, adrenals, heart, trachea, pituitary		9	CMV, MAC, KS	19

65*	AIDS		<100	No	No	Yes	Asymptomatic	Lungs, liver, spleen, LN, eye (choroid), kidneys, small intestines	TMP-SMX, TMP-D	75	CMV, MAC	140
66*	AIDS	Homo	35	No	No	Yes (probably)	Lower-extremity edema, abdominal distension, diarrhea	Lungs, liver, spleen, LN, pancreas	None	1	MAC	108
67*	AIDS	Homo		Yes	Yes (16)	Yes (probably)	Pneumonia	Lungs, liver, spleen, LN, thyroid, eye (choroid), adrenal, heart, GI tract	i.v. P → TMP-D	14		136
68*	ARC	IVDU			No	Yes	Pneumonia	Lungs, liver, spleen, LN, vessels	TMP-SMX	3		1
69*	AIDS	Tx		Yes (×4)	Yes (6)	Yes	Toe necrosis	Lungs, liver, spleen, LN, vessels, thyroid, kidneys, adrenals, heart, brain, GI tract		13		23
70*	AIDS	Tx		Yes	Yes (16)	Yes	Dyspnea, pulmonary edema	Lungs, liver, spleen, bone marrow, thyroid, eye (choroid), adrenal, heart, GI tract		20		103
71*	AIDS	Homo	188 (1 yr PTA)	Yes (×2)	Yes (8)	Yes	Retinitis (CMV), fever	Lungs, liver, spleen, bone marrow, vessels, thyroid, kidneys, adrenals, pancreas, parathyroid		15	*C. neoformans*	18
72*	AIDS		6.5		Yes (18+)	Yes		Lungs, liver, spleen, eye (choroid), kidney, heart, pancreas	TMP-SMX	Died		87
73	AIDS		30	No	Yes (14.5)	Yes	Dyspnea, fever, abdominal distension	Lungs, liver, spleen, kidney	TMP-SMX	365	CMV	141
74*	AIDS	IVDU	6	Yes (×1)	Yes (12)	Yes	Ascites, edema, liver failure, splenomegaly	Lungs, liver, spleen, vessels	None	1		6
75*	AIDS		3	No	Yes (21)	Yes	Fever, weight loss	Lungs, liver, spleen, vessels, thyroid, kidney, adrenals, heart, pancreas	i.v. P	2	MAC	6
76	AIDS			Yes (×2)	Yes (12)	Yes	Acute right-sided chest pain, dyspnea	Lungs, pleura, vessels	AP	Died	KS	28
77	AIDS	Homo		Yes (×2)	Yes (12)	Yes	Fever, chills, dyspnea, cough	Lungs, pleural effusions (bilateral)	i.v. P	Survived		104
78*	ARC	Homo		No	No	Yes	Fever, dry cough, mild dyspnea, weight loss	Lungs, retina	TMP-SMX + i.v. P	19		66
79			6.5		Yes (18+)	Yes		Lungs, spleen	Clindamycin-primaquine	Survived		87
80	AIDS	Homo		Yes	Yes	Yes	Cough, fever	Lungs, spleen, LN	i.v. P	14		115
81*	AIDS	Homo		Yes (×3)	Yes	Yes	Fever, dyspnea	Lungs, spleen, LN, adrenals		30	MTb, HepB, GC, cryptosporidia	19
82*	AIDS	Homo		Yes (×3)	No	Yes	Decreased visual acuity, progressive confusion, severe dyspnea, decreasing urine output	Lungs, spleen, LN, bone marrow, adrenals		6	*C. neoformans*, KS	129
83*	AIDS	Homo		Yes (mult)	No	Yes	Dyspnea, altered mental status	Lungs, spleen, LN, bone marrow, adrenals		Died	CMV, *C. neoformans*, KS	19

TABLE 1—*Continued*

Case no.[b]	HIV diagnosis	Risk factor	Peripheral CD4 count (no/μl)	Previous PCP	Previous AP (duration [mo])	Concurrent PCP	Symptom(s)	Site	Drug therapy	Survival (days)	Other opportunistic infections or cancers	Reference
84*	ARC	Homo		No	No	Yes	Fever, fatigue, lymphadenopathy, left upper quadrant abdominal pain	Lungs, spleen, bone marrow, LN, thyroid, eye (choroid), kidney, adrenals, heart, GI tract, pancreas, ureter	TMP-SMX	14		74
85*	AIDS	Tx				Yes	Fever	Lungs, lumens of blood vessels	None		CMV	132
86*	AIDS	Homo		Yes	Yes (36)	Yes	Fever, dyspnea, weight loss	Lungs; lumen of the hepatic, renal, and adrenal blood vessels		9		141
87	AIDS		6.5		Yes (18+)			Liver, spleen		Survived		87
88	AIDS			Yes	Yes	No	Decreased vision (both eyes)	Eye (choroid), bone marrow	i.v. TMP-SMX	Alive at 4 wk		120
89*		Homo		No	No	No	Left upper quadrant abdominal pain	All organs at autopsy	i.v. TMP-SMX, i.v. P	30	CMV, HSV	122
90*	AIDS			Yes (×1)	No	Yes (probably)		Widespread		11	*M. kansasii*	41

[a] Abbreviations: OI, opportunistic infections; AP, aerosolized pentamidine; IVDU, intravenous drug user; Homo, homosexual; Bisex, bisexual; Tx, transfusion recipient; HIV^+, HIV seropositive; mult, multiple; →, change (in anti-pneumocystis therapy); D, dapsone; P, pentamidine; HSV, herpes simplex virus; PML, progressive multifocal leukoencephalopathy; MAC, *Mycobacterium avium* complex; KS, Kaposi's sarcoma; MTb, *Mycobacterium tuberculosis*; HepB, hepatitis B virus; GC, *Neisseria gonorrhoeae*; LN, lymph nodes; GI, gastrointestinal; PTA, prior to admission; pyri, pyrimethamine; qw, once a week. Spaces are left blank if the information of interest was not reported.

[b] Asterisks indicate patients who were examined at autopsy.

(b) Eye (choroid layer). Ocular pneumocystosis was typically localized to the choroid layer (as opposed to the retina or sclera).

A single case of pneumocystosis apparently restricted to the choroid layer of the eye only has been reported (Table 1, case 10). This patient had never had a previous episode of PCP, had never received aerosolized pentamidine prophylaxis (although the patient's peripheral $CD4^+$ lymphocyte count was 12/μl at the time of presentation, he had been diagnosed as HIV-1 seropositive only 1 month before presentation), was successfully treated with dapsone-TMP for 21 days, and survived for at least an additional 21 months.

Seven cases of ocular (choroidal) pneumocystosis were reported in patients who lacked concurrent PCP but who had had at least one previous episode of PCP (Table 1, cases 11 to 18). All seven patients had received prophylactic aerosolized pentamidine for secondary PCP (mean, 10 months; range, 1 to 26 months). Peripheral $CD4^+$ lymphocyte counts were available for only three patients and were 36, 10, and 38/μl, respectively. The patient with a peripheral $CD4^+$ lymphocyte count of 36/μl presented 26 months after a previous episode of PCP, had received prophylactic aerosolized pentamidine for 26 months, was not treated, and died 14 days later. The patient with a peripheral $CD4^+$ lymphocyte count of 38/μl presented 2 months after a previous diagnosis of PCP, had received prophylactic aerosolized pentamidine for 1 month, was treated successfully for the acute ocular choroiditis, was treated prophylactically with dapsone-TMP, and was still alive 10 months later. All of the remaining six patients survived their ocular pneumocystosis. The length of time for survival was reported for only two of these five patients, who survived for 1 and 1.5 years, respectively. Their ultimate causes of death were not reported.

Four additional cases of ocular (choroidal) pneumocystosis have been reported (Table 1, cases 19 to 22), but whether the disease was in fact limited to this site was unclear because of a lack of clinical information about previous episodes of PCP, previous prophylaxis, or whether PCP was concurrently present at the time of presentation (109). Information on prophylaxis with aerosolized pentamidine was available for only one of the four patients (Table 1, case 19), who had received prophylaxis for 8 months prior to presentation. Survival was reported for only three of the patients, who were still alive at 1, 4, and 6 months, respectively, after presentation.

Symptoms of ocular (choroidal) pneumocystosis ranged from none to nonspecific complaints (e.g., "floaters" or visual field loss). For patients lacking ocular symptoms, choroidal pneumocystosis was usually diagnosed by the "characteristic" appearance of *P. carinii* choroiditis on routine ophthalmologic examination (i.e., "multiple focal circumscribed creamy to yellow-white round or oval deep choroidal lesions without overlying or surrounding inflammation or involvement of other ocular structures" [116]).

Ocular (choroidal) lesions were successfully treated with intravenous (i.v.) or oral TMP-SMX or dapsone-TMP or i.v. pentamidine with complete resolution of symptoms or, if asymptomatic, of lesions.

(c) Thyroid. Three cases of extrapulmonary pneumocystosis seemingly restricted to the thyroid have been reported (Table 1, cases 23 to 25). All three patients had a diagnosis of AIDS at the time of presentation, and only one had received aerosolized pentamidine prophylaxis. All three patients presented with thyromegaly, and two of them were treated successfully with TMP-SMX. The third patient (78) was not initially treated because diagnostic tissue obtained from the

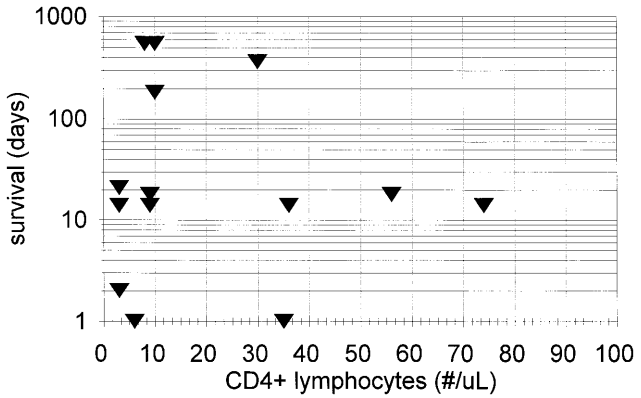

FIG. 2. Survival of HIV-infected patients with extrapulmonary pneumocystosis relative to peripheral $CD4^+$ lymphocyte count.

"neck mass" by fine-needle aspiration was examined only for acid-fast bacilli. This patient returned 6 weeks later with severe abdominal pain caused by small bowel perforation and concomitant PCP; despite surgical correction of the perforation, the patient died 7 days after presentation. Postmortem examination revealed pneumocystis in the lungs, liver, spleen, kidneys, abdominal lymph nodes, small bowel wall, and thyroid.

(d) Spleen. At least two cases of pneumocystosis in the spleen have been reported (Table 1, cases 26 and 27). Both patients lacked concurrent PCP (each had a diagnosis of AIDS, but only one had received aerosol pentamidine prophylaxis), and no information on previous episodes of PCP was reported. Symptoms were related to splenomegaly. Both patients survived following i.v. pentamidine therapy.

(e) Miscellaneous sites. (i) Pleural effusion. A single case of a pleural effusion containing *P. carinii* in the absence of PCP has been reported (Table 1, case 28). The patient had had PCP 18 months earlier and had received therapy with aerosolized pentamidine for at least 20 months. Treatment with TMP-SMX was successful, and the patient survived for an additional year.

(ii) Bone marrow. A single case of pneumocystosis limited to the bone marrow has been reported (Table 1, case 29). The patient had a diagnosis of AIDS, had never received prophylactic aerosolized pentamidine, presented with pancytopenia, and died 30 days later despite therapy with i.v. pentamidine.

(iii) Muscle. A single case of pneumocystosis limited to the right thigh has been reported (Table 1, case 30). The patient had cytomegalovirus (CMV) retinitis and a peripheral $CD4^+$ lymphocyte count of 49/μl, received prophylactic aerosolized pentamidine therapy for 30 months, and never had a prior episode of PCP. He presented with complaints of muscle spasms, pain, and swelling in his right thigh. Biopsy of the afflicted area revealed granulomatous inflammation and *P. carinii*; he was treated with TMP-SMX and experienced resolution of the thigh pain and swelling. He died 5 months later from disseminated *Mycobacterium avium* complex infection.

(iv) Meninges and cerebral cortex. A single case of pneumocystosis restricted to the meninges and cerebral cortex was reported in a patient who had been diagnosed with cryptococcal meningitis 8 months earlier (Table 1, case 31). He presented at clinic complaining of headache, fever, cough, and nausea and was found dead at home 1 day later. A postmortem examination revealed cryptococci and *P. carinii* in the cerebral cortex and meninges without evidence of pneumocystosis elsewhere.

(v) Gastrointestinal tract. A single case of pneumocystosis in the cecum and descending and sigmoid colon has been reported (Table 1, case 32). The patient had received a diagnosis of AIDS 2 years before presentation based on evidence of Kaposi's sarcoma. He presented with diarrhea that resolved with i.v. therapy (originally TMP-SMX and then pentamidine, because of TMP-SMX intolerance, for a total of 21 days). Of interest, he complained of blurred vision on hospital day 16, and an ophthalmologic examination revealed ocular choroidal lesions characteristic of *P. carinii* choroiditis that subsequently diminished with his ongoing therapy for gastrointestinal tract pneumocystosis.

(ii) At multiple noncontiguous sites. Many of the patients discussed above who had extrapulmonary pneumocystosis apparently restricted to a single site survived their initial episode and were lost to follow-up; only three (9%) of the 32 patients underwent a postmortem examination at the time of death. The possibility that clinically asymptomatic extrapulmonary pneumocystosis was also present in these individuals could not be excluded. In contrast, 29 (50%) of the 58 patients with extrapulmonary pneumocystosis at multiple noncontiguous sites (Table 1, cases 33 to 90) underwent postmortem examination. The careful examination of all organs at autopsy might have revealed clinically inapparent *P. carinii* in organs or tissues, thus exaggerating the clinical significance of widespread extrapulmonary disease.

At least 43 (74%) of the 58 cases of extrapulmonary pneumocystosis at multiple noncontiguous sites occurred in patients who had concurrent PCP; at least 12 (28%) of the 43 patients with concurrent PCP had never had a previous episode of PCP. At least 16 (28%) of the 58 patients had never received aerosolized pentamidine prophylaxis.

The presenting symptoms were quite variable and included fever, cough, dyspnea, abdominal pain, abdominal distension, hepatitis, anasarca, dysphagia, chest pain, and altered mental status.

Based on the autopsy findings from a number of cases, dissemination could have occurred by direct spread or by hematogenous or lymphatic routes. Of the 58 reported patients with extrapulmonary pneumocystosis, 1 was a patient who had concurrent PCP and had *P. carinii* detected in the pleura (Table 1, case 76); this contiguity of the pleura with the infected lungs would suggest that local spread of *P. carinii* had occurred. Evidence of hematogenous spread in-

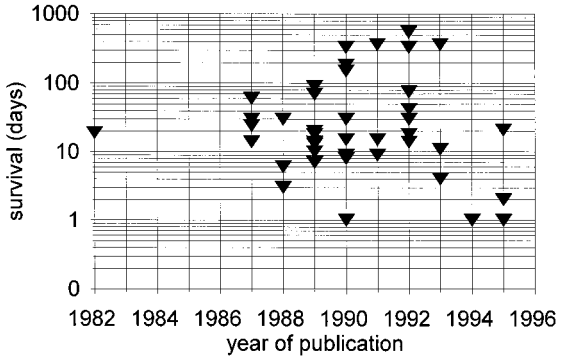

FIG. 3. Length of survival of HIV-infected patients with extrapulmonary pneumocystosis relative to year of publication.

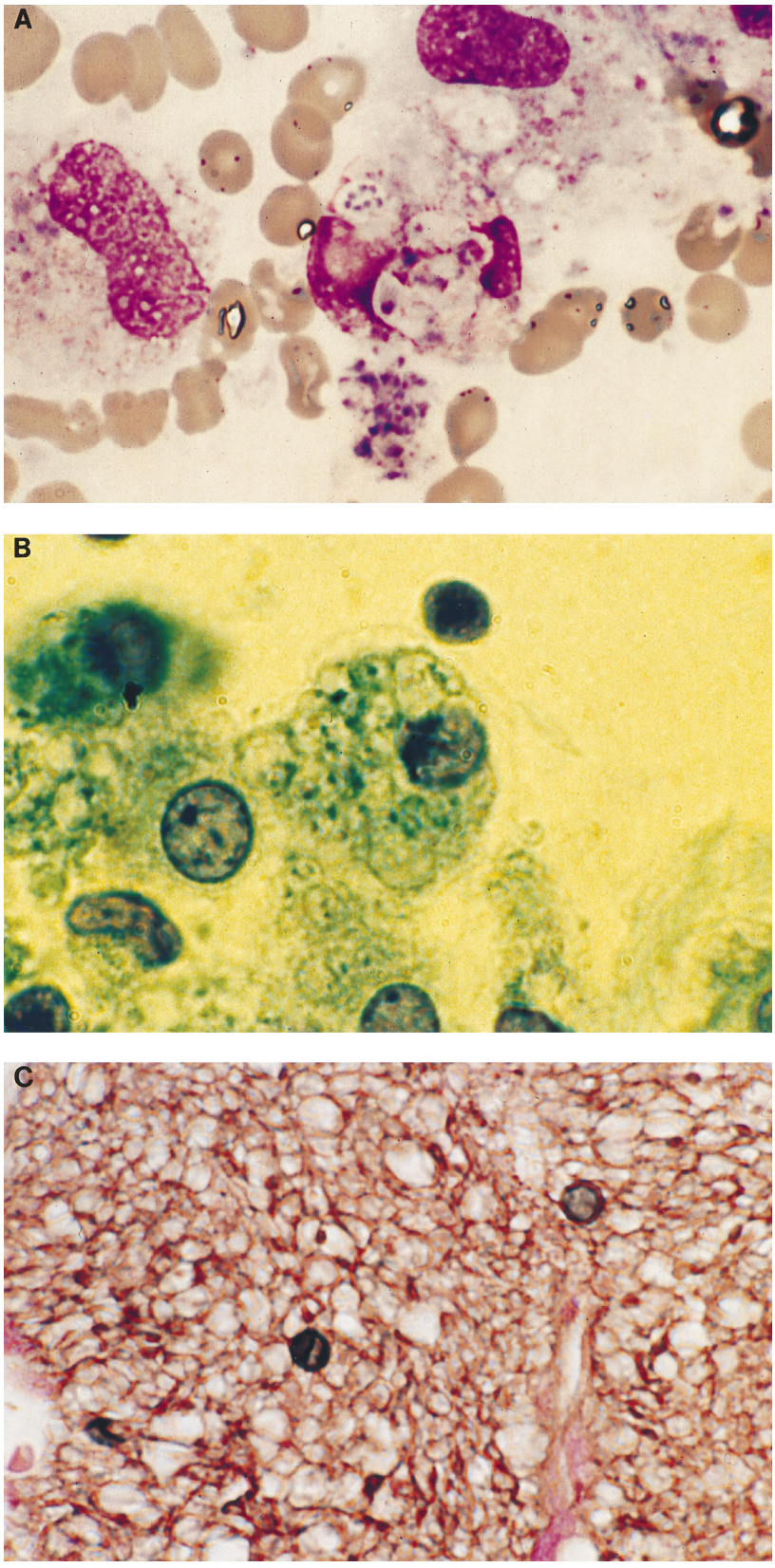

FIG. 4. *P. carinii* in bone marrow. (A) Giemsa-stained bone marrow aspirate preparation (magnification, ca. ×1500). Note the clump of *P. carinii* trophic forms (i.e., acidophilic pink cytoplasm and small purple nuclei) to the right of the marrow cells. (B) GMS-stained bone marrow aspirate preparation (magnification, ca. ×1500). Note four *P. carinii* cysts with intensely stained (i.e., black) cyst walls and cyst wall "double bodies." (C) GMS-stained, formalin-fixed, paraffin-embedded bone marrow biopsy specimen (magnification, ca. ×700). Note two silver-stained *P. carinii* cysts.

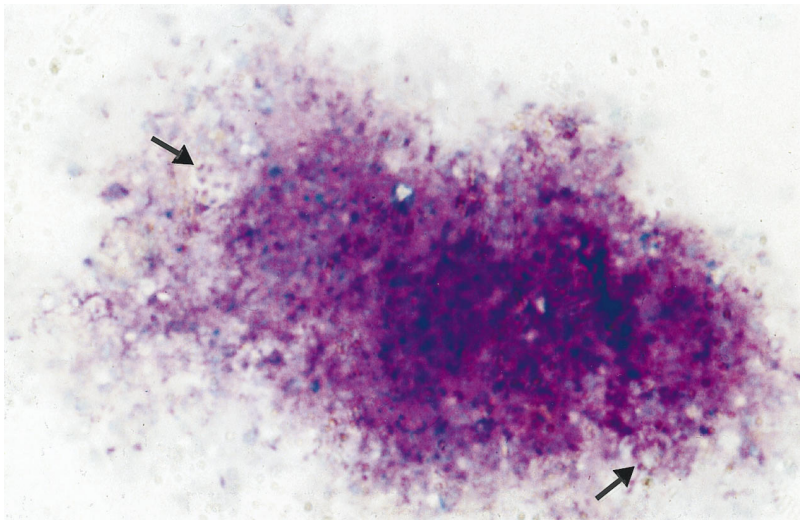

FIG. 5. *P. carinii* in the middle ear. A Giemsa-stained middle ear fluid aspirate (magnification, ca. ×1500) is shown. Note the clump of adherent *P. carinii* trophozoites and cysts, some with well-defined intracystic bodies (at the tips of the arrows).

cluded the finding of emboli consisting of *P. carinii* and associated eosinophilic matrix in the lumens of numerous large blood vessels at the time of autopsy in numerous patients with extrapulmonary pneumocystosis; it was especially dramatic in the single case of a patient who presented with necrotic toes secondary to *P. carinii* emboli (Table 1, case 69 [23]). Similarly, the relatively common finding of *P. carinii* in nonthoracic lymph nodes in numerous patients with extrapulmonary pneumocystosis provides evidence of lymphatic spread. Fifty-eight patients with extrapulmonary pneumocystosis (Table 1, cases 33 to 90) had *P. carinii* at multiple noncontiguous sites, including the retina, eye (choroid layer), liver, spleen, lymph nodes, gastrointestinal tract, lumen of blood vessels, thyroid, pancreas, kidney, ureter, bone marrow, adrenals, heart, trachea, pituitary, ascitic fluid, urine, parathyroids, diaphragm, and paraspinous masses. Patients who died within 30 days after presentation tended to have a greater number of infected sites.

Diagnosis

The diagnosis of extrapulmonary pneumocystosis is straightforward once it is considered in the differential diagnosis. It is rarely considered, however (and perhaps appropriately), given its low frequency of occurrence coupled with the protean nonspecific symptoms that could be attributable to a variety of other infectious organisms or diseases (e.g., *Mycobacterium avium* complex, cryptococcosis, and lymphoma) that occur more commonly in patients with advanced HIV-1-associated disease. Nonetheless, clinical consideration of disseminated disease and subsequent acquisition of a diagnostic specimen (either fluid drainage or diagnostic tissue obtained by surgical or invasive procedures) from the affected site are the two most important factors in establishing a diagnosis.

Extrapulmonary pneumocystosis is diagnosed by the demonstration of *P. carinii* cysts or trophozoites in affected tissues. In many of the published cases, detection of *P. carinii* was an "incidental" finding made by the clinical microbiologist or pathologist. Thus, the clinical microbiologist or pathologist is often the key individual to establish the diagnosis and must therefore be able to recognize the foamy eosinophilic material in which *P. carinii* cysts and trophozoites are typically embedded (Fig. 4 to 6) and must confirm the diagnosis by performing additional stains, if necessary (e.g., Gomori-methenamine-silver (GMS), Giemsa, or rapid Giemsa-like stains such as Diff-Quik, toluidine blue O, immunofluorescent stains with monoclonal anti-pneumocystis antibodies), that reveal the characteristic morphology of the cyst and/or trophic forms (Fig. 4 to 6). All stains have comparable sensitivity for the detection of pneumocystis (21, 43, 83, 84).

For the majority of cases summarized in this review, extrapulmonary pneumocystosis was diagnosed by detection of *P. carinii* cysts in GMS-stained, formalin-fixed tissue (obtained during biopsy or autopsy). A few cases of ocular (choroidal) pneumocystosis were diagnosed clinically based on the characteristic appearance of the lesions and reduction or eradication of lesions in response to appropriate therapy. Only a few cases of extrapulmonary pneumocystosis were diagnosed by detection of *P. carinii* in Giemsa-stained material; these cases were restricted to patients who had pneumocystis in the various body fluids (e.g., ascites, pleural fluid, or ear discharge) that would normally be examined in a clinical laboratory.

There is some concern that pentamidine therapy might alter the staining characteristics of pneumocystis based on a study which reported abnormal staining and subsequent difficulty in diagnosing PCP in patients who had received prophylaxis with aerosolized pentamidine (61). Abnormal staining of pneumocystis organisms from patients receiving aerosolized pentamidine, however, was not observed in three other studies (71, 79, 82).

Previously published cases have demonstrated that a large burden of *P. carinii* resides in the affected tissues of patients with extrapulmonary pneumocystosis. Thus, histologic examination alone of affected tissues is sufficient for diagnosis. Given the large extrapulmonary tissue burden of organisms, sensitive detection techniques, such as PCR, should theoretically not be necessary for diagnosis. One recent study in a rat model system, however, demonstrated complete concordance of ex-

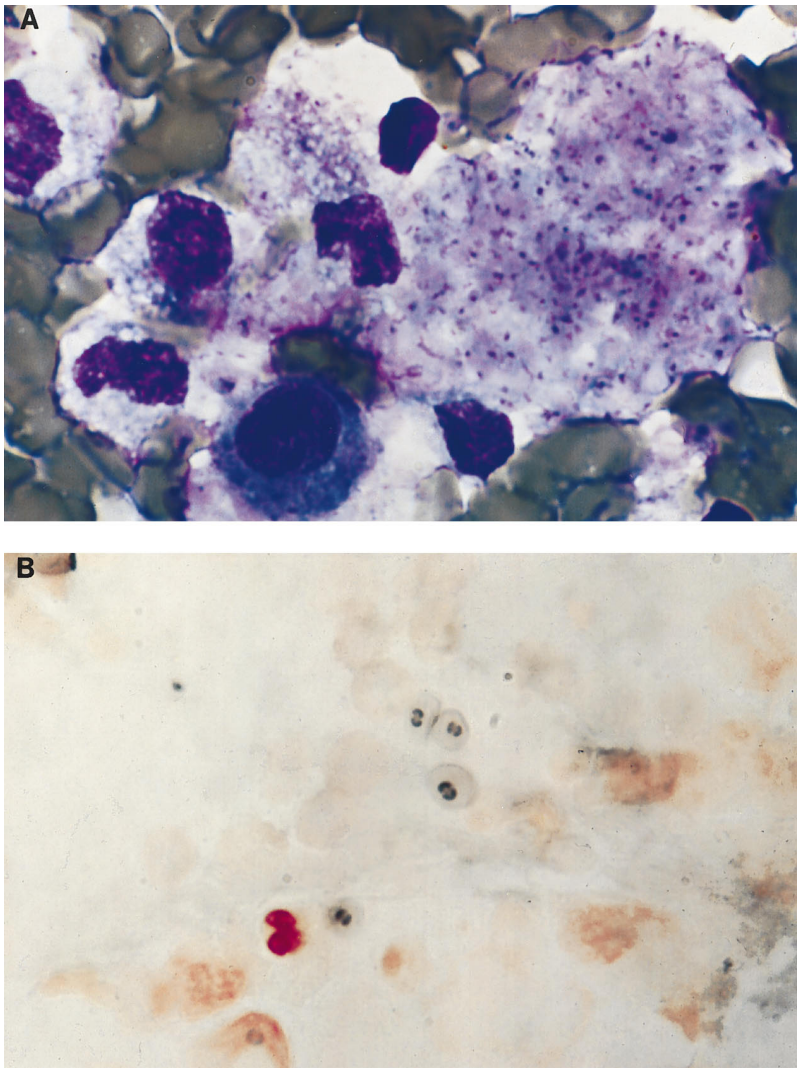

FIG. 6. *P. carinii* in pleural fluid. (A) Giemsa-stained pleural fluid (magnification, ca. ×1500). Note the *P. carinii* cysts with intracystic bodies and trophic forms ingested by adjacent macrophages. (B) Papanicolaou-stained (Pap) pleural fluid (magnification, ca. ×1500). Note the *P. carinii* trophic forms ingested by the macrophage.

trapulmonary pneumocystosis with heminested PCR detection of *P. carinii* dihydrofolate reductase gene transcripts in affected nonpulmonary tissues (15).

Since the morphology of the cyst and trophic forms is characteristic in extrapulmonary pneumocystosis as well as in PCP, there is no obvious need for additional methods of definitive identification. One small autopsy series used immunohistochemical staining with monoclonal anti-pneumocystis antibodies to formally identify the GMS-stained cystic material observed in various organs as *P. carinii* (25). However, the characteristic morphology demonstrated by the GMS stain was, in retrospect, adequate for diagnosis.

Treatment

A variety of antipneumocystis agents were used to treat extrapulmonary pneumocystosis. No single therapeutic regimen was clearly associated with either a better or worse outcome.

A recent report described an AIDS patient who had hepatic and splenic pneumocystosis that failed to resolve after 2 months of daily therapy with i.v. TMP-SMX (4.8 g) yet subsequently had a clinical, radiologic, and biological response to 3 weeks of i.v. pentamidine therapy (3 mg/kg) (67). Although *P. carinii* was detected in the peripheral blood of this patient by PCR throughout the entire 2 months of treatment with i.v. TMP-SMX, PCR did not detect *P. carinii* in the peripheral blood within days after the i.v. pentamidine therapy was started. The authors concluded that the strain of *P. carinii* infecting this patient was resistant to TMP-SMX and speculated that strains of *P. carinii* responsible for extrapulmonary pneumocystosis may be different from strains that cause pneumonia, raising the possibility that such genetic variants also differ in their antimicrobial susceptibility.

Conclusions

Extrapulmonary pneumocystosis is a rare disease. In non–HIV-1–infected individuals, disseminated disease often occurred immediately premortem; patients usually died of their underlying disease, and extrapulmonary pneumocystosis was not clinically evident. For HIV-1-infected individuals, extrapulmonary pneumocystosis limited to the eye (choroid layer) or ear had a better prognosis than disseminated pneumocystosis in multiple noncontiguous sites. The latter was usually clinically evident, with symptoms related to the affected organs. Disseminated disease often occurred during the terminal stage of HIV-1-related disease, and peripheral $CD4^+$ lymphocyte counts were not predictive of survival.

Many of the reported cases occurred during an era when aerosolized pentamidine was in wide use for primary or secondary PCP prophylaxis. Although there was much speculation that the apparent increase in extrapulmonary pneumocystosis cases in HIV-1-infected individuals might be related to the lack of adequate pentamidine levels in the peripheral blood, reports of subsequent cases of extrapulmonary pneumocystosis occurring in individuals receiving systemic prophylaxis with dapsone and pyrimethamine suggest that other, as yet unidentified factors may play a role in dissemination.

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